REMARKS

The claims are not obvious under 35 USC §103

Claims 1-4, 6-16, 18-26, 28-31 and 33-35 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the Bankneider *et al.* reference, in light of the York reference. Applicants respectfully contend the above amendments to the claims overcome the Examiner's rejections.

Applicants respectfully contend that the cited art, taken alone or in combination, contain no teaching, suggestion or motivation to use compounds (ARIs) known and used for internal purposes (systemic treatment of wounds) or ophthalmic wound treatment, to topically treat skin wounds. Bankneider *et al.* teaches a method of *systemically* treating wounds with tolrestat. There is no indication in the Bankneider reference that treatment can be accomplished by topical administration. There is a significant, art-recognized difference between the topical treatment of wounds and the systemic treatment of wounds in terms of delivery, carriers, dosage, efficacy, and toxicity. Orally-administered drugs are absorbed quickly and dispersed through the body to diverse tissues having differential sensitivity to the drug, and some tissues such as liver are particularly sensitive to certain drugs because the portal circulation delivers a relatively much higher dose of the drug to that organ immediately after adsorption through the intestines. Thus, certain drugs are unsuitable for oral administration.

On the other hand, certain other drugs are unsuitable for epidermal administration. The skin acts as a protective barrier against the environment, and against loss of water, protein, electrolytes and heat. While topical treatment may be an attractive alternative for treatment of certain maladies, not all treatments are amenable to topical use. For example, while acne may be treated topically, systemic treatment is far more effective. It may be impractical to deliver an effective dose via topical treatment, because of the relative impermeability of the skin, resulting in extremely high concentrations of a treatment compound to be present in order to deliver an effective concentration of the drug. The Bankneider reference contains no teachings on these distinctions, and is limited solely to systemic administration.

York teaches the use of aldose reductase inhibitors for treating wounds of the eye. There is no indication in York that wounds of the skin may be treated topically. The eye is recognized, both in common experience as well as in the art, as being a quite specialized tissue having distinctive

properties that are unique thereto. It would not have been obvious to one skilled in the art that treatments for ophthalmic wounds would necessarily work for treatment of skin wounds. Moreover, the Office has cited no reference that teaches that treatments specific for the eye could be useful in topical administration to the skin.

The claims, as amended, are directed toward treatment of wounds of the dermis or epidermis, not ophthalmic wounds. The treatment of dermal and epidermal wounds is not taught by York. Additionally, the permeability of the skin is vastly different from the permeability of the eye. Therefore, it is not obvious that a treatment used topically in the eye could be used to topically treat wounds of the skin. York itself makes no suggestion that treatments which work for ophthalmic wounds would work for dermal or epidermal wounds.

The combination of the references does not disclose or enable practice of the invention as instantly claimed. *In re Dance*, 160 F.3d 1339 (Fed. Cir. 1998) (In order to establish such a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant). Further, the Office has provided no evidence that "one having ordinary skill in the art *would have been led* to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention" and has thus failed to meet the burden required to make a *prima facie* case of obviousness. *Ex parte Levengood*, 28 USPQ2d 1300, 1301 (Bd. Pat. App. & Int'f. 1993). Based on the foregoing, Applicants respectfully contend that the asserted obviousness rejection has been traversed by their argument and respectfully request that the Examiner withdraw this ground of rejection.

Claims 1-4, 6-7, 13-16, 18-19, 25-26, 28-31, and 33-35 stand rejected under 35 U.S.C §103 in light of York and FDA Guideline No. 38. Applicants argue that the claims, as amended, are not obvious in light of York in view of FDA Guideline No. 38.

As discussed above, York merely discloses the topical administration of aldose reductase inhibitors for treatment of ophthalmic wounds. York fails to disclose the treatment of *skin* wounds by aldose reductase inhibitors. Furthermore, York does not suggest that ophthalmic treatments may be used for treatment of skin wounds.

The Office cites FDA Guideline No. 38, claiming that Guideline No. 38 discloses comparing the efficacy of test compositions for treatment of animals against other known or potentially useful agents. The Office has cited Chen *et al.* as an example of the utilization of Guideline No. 38 for such a comparison. However, the cited sections of Guideline 38 discuss dose determination and testing procedures for topical/otic (used near the ear) preparations used to treat animals. Specifically, Section IX of Guideline No. 38, Testing Procedures for Combination Topical/Otic Preparations, suggests the use of controls to study the efficacy of each component of a combination drug. One such control, referred to as Group I, would presumably be a no-treatment control. Groups II-V include various combinations of components, combined to test the efficacy of each component in combination with one or more other components. However, Section IX does not teach the comparison of any combination of components against other potentially useful agents, as suggested in the Official Action, mailed October 7, 2005 (p.3). Contrary to the position taken in the Action, Guideline No. 38 does not suggest comparing various similar drugs or other potentially useful agents, but rather merely suggests controls to determine the efficacy of components of 3-way and 2-way combination treatments, to assure that each component of the combination is effective.

To the extent that aspects of the claimed invention share features disclosed in Guideline No. 38 (*for example*, using a no-treatment control), this does not cure the deficiencies of this reference because, first, this is a commonly-used control step and second, more importantly, the reference does not disclose or even suggest the compound to be tested.

The Chen reference is cited in the Action to establish that the methods disclosed in Guideline No. 38 are well-known in the art. This misses the point: while the reference may illustrate a commonly-used control step, neither the Guideline nor the Chen reference fulfills the requirements of rendering the instantly-claimed invention obvious, *i.e.*, providing teaching, suggestion or motivation that they themselves be combined, and when so combined, providing teaching, suggestion or motivation to achieve the claimed invention *coupled with* a reasonable expectation of its success. Chen does not remedy the fact that neither York nor Guideline 38 provides any motivation for one skilled in the art to apply the ophthalmic treatment disclosed in York for treatment of skin wounds. Furthermore, there is no motivation in any of the three references to make the combination of these references, nor would a combination of the references result in the teaching of the presently claimed invention, namely the topical treatment of skin wounds with aldose reductase inhibitors.

Applicants respectfully contend that the cited art, taken alone or in combination, contains no teaching, suggestion or motivation to use the claimed method to identify aldose reductase inhibitors which improve wound healing in a diabetic animal, nor to use the compounds identified by the claimed method to treat skin wounds in a diabetic animal. Applicants further respectfully contend that the cited prior art, properly limited to what it does and does not teach, does not support rejection of any of the rejected claims under 35 U.S.C. §103(a).

Based on the foregoing, Applicants respectfully contend that the asserted obviousness rejection has been traversed by their arguments and amendments and respectfully request that the Examiner withdraw these grounds of rejection.

CONCLUSION

It is believed that all requirements of patentability are fully met, and allowance of the claims is respectfully requested. If the Examiner believes it to be helpful, the Examiner is invited to contact the undersigned attorney by telephone at 312-913-0001.

Respectfully submitted,

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Date: January 9, 2006